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EDITORIAL

Keith Wesnes: Psychopharmacology pioneer

Keith Wesnes passed away earlier this year. Among those of us who knew him, or knew of him, his absence from this planet has caused sadness. It also caused us to reflect on his noble life in science and how his ideas continue to bounce around our little corner of the cosmos. There is no doubt that Wesnes and his collaborators revolutionized approaches to the measurement of cognition in understanding the central nervous system (CNS) effects of both licensed and experimental drugs. The innovative and creative genesis of his approach are evident in his initial work. Figure 1 re-plots the data from Wesnes and Warburton (1983)[1] which observed that an acute 1.2 mg (p.o.) dose of scopolamine was associated with a substantial decline (ie, d ~0.69) in rapid information processing. Three aspects of this finding illustrate Keith's elegant approach to psychopharmacology and how it influences us today.

First, Keith's ideas were prescient in that he appreciated the benefits of computer hardware and software in controlling the design and execution of cognitive challenges, as well as the presentation of visual and auditory stimuli and capture of manual responses. The group mean data in Figure 1 reflects performance on a computer-controlled measure of rapid information processing. Psychological models of the time were influenced heavily by electronic circuit boards and their application as processors in computing.[2] Thus, the poetry in this figure is that Keith was using an electronic rapid information processor to understand a biological rapid information processor by seeking to interfere with its function using anticholinergic drugs. The serial nature of the guiding theoretical model is emphasized in the discussion in which the authors speculate as to whether findings of adverse memory effects related to scopolamine were in fact secondary to the effects of the drug on information processing. While we no longer view the CNS as a circuit board, it is still the case that scopolamine interferes with the ability of the CNS to maintain attention at approximately the same magnitude of effect at equivalent doses across delivery systems (eg, subcutaneous, vs. p.o.).[3] We also continue to debate the extent to which the effects of scopolamine on higher cognitive functions such as memory are secondary to its deleterious effects on alertness and arousal.[4]

Second, the data drawn in Figure 1 represent the effects of the experimental drugs expressed as change from baseline. Not just that, but these data were generated from a four-period double-blind placebo-controlled cross-over design. While within-subjects designs are common now, around 1983 most pharmacological–cognitive models were based on between-group comparisons. Keith was one of the first to recognize that drug effects on cognition manifest differently in each individual and that there were substantial benefits to experimental precision and the resultant theoretical models when such variation was controlled. However, as the effects of these anticholinergic drugs occurred rapidly and required multiple repeated measurements to characterize fully, these cross-over designs required that this testing regimen be given in multiple experimental sessions. By harnessing the power of the relatively new personal computer Keith was able to conduct the necessary high-frequency testing at very short retest intervals in large numbers of subjects in multiple periods with a modest demand on resources. Most cognitive models of CNS function are still based on data from single assessments, with comparisons made between experimental groups or to normative data. Keith showed us that computers could be used to magnify signals of cognitive change, affording powerful new ways to understand, validate, and confirm change in CNS function. By measuring such change, even over very short retest intervals, a new sophistication in brain–behavior models was possible.[5] His frustration with the persistent use of paper-and-pencil tests, with all their imprecision, and often their learning effects that obscure signals, was expressed energetically and frequently to anyone who would listen.

The third important aspect of Keith's science is that he had substantial skin in the game. He believed sufficiently in his ideas and their operationalization that, rather than pursuing a conventional academic or clinical career he went directly to industry. While Figure 1 is about scopolamine, Figure 2 in the original publication shows the effects of nicotine within the same model; work designed obviously as part of a program to understand the psychopharmacological effects of cigarette smoking. Extending on this work Keith started a business in which he provided his tools and their theoretical contexts to companies and researchers so they could utilize these to guide decisions about the safety and the efficacy of other CNS-active drugs. Much is now made of the "crisis of replication" for experiments in both psychology and drug development.[6] Keith's business straddled both domains and its successes were dependent on the ability of his models and his tools to replicate; indeed, to replicate and extend. If customers engaged him and his company's services, and their experiments did not work as predicted, then there would be no repeat business. In this context

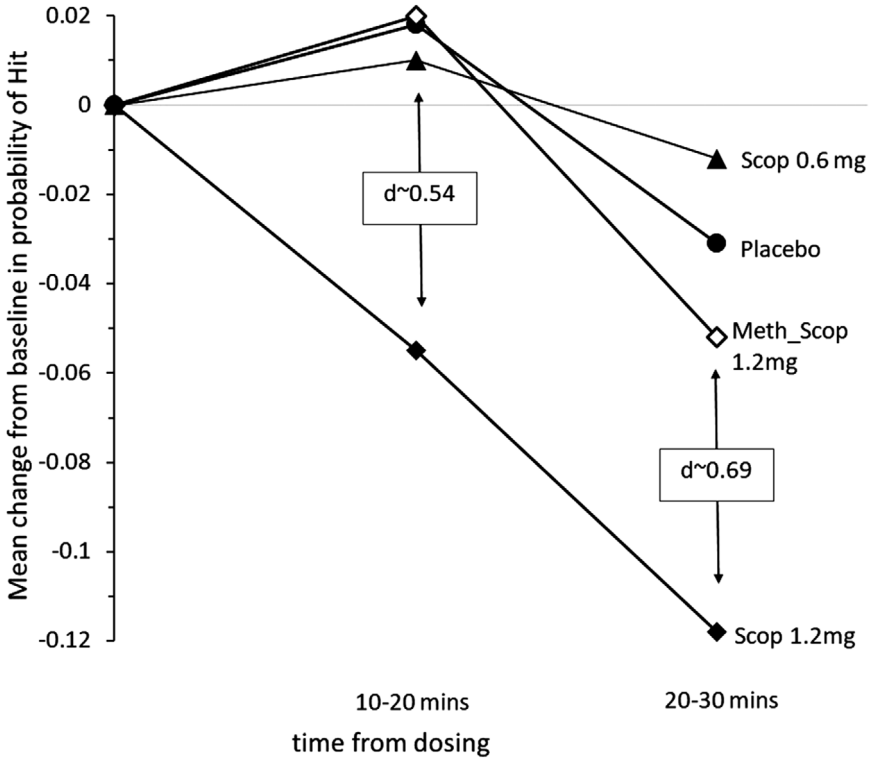

FIGURE 1 Group mean change from a pre-treatment baseline in hit rate (correct identifications of three consecutive odd or three consecutive even digits) from a string of digits presented at a rate of 100/s prior under scopolamine 0.6 mg (p.o.) or 1.2 mg (p.o.), meth-scopolamine 1.2 mg (p.o.) or placebo for 12 subjects who completed each condition in a four-way cross-over design. The value for d shown in the figure is the estimated effect size for the difference between means for the scopolamine 1.2 mg and placebo condition at each post-baseline assessment (assuming test-retest correlation = 0.7)

of required rigor, Keith's approach flourished. He went on to develop a successful business that was involved directly and indirectly in the regulatory approval of multiple medicines for CNS disease. However, he also gave us more than 250 publications in peer-reviewed scientific journals, trained and mentored many psychopharmacologists, and increased dramatically the world's understanding of the importance of cognitive assessments in drug development programs.

Keith Wesnes' life in science has been for us a star to navigate by; we have benefited enormously from our competition, collaboration, and friendship. It was good to see him in recent years after he relinquished the helm of his remarkable enterprise, more relaxed than before, yet every bit as formidable intellectually, and as fully as engaged and determined to advance the field whose scientific foundation he single-handedly created. Despite his passing, these accomplishments, the challenges he then issued to us, and his jokes and humorous misadventures remain large today and we are all richer for that.

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